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(54) **Tooth whitening compositions containing both chlorite and chlorate salts**

(57) Peroxide-free tooth-whitening compositions (e.g. toothpastes) comprise both 1% - 5% chlorate salts and 0.5% - 25% of chlorite salts, preferably in the synergistic ratio of 5:5 to 5:2. The compositions have a slightly acidic pH, in the range of 6 to 7, and may also have an oxidation-resistant proteolytic enzyme. Other ingredients include a biostat such as propylene glycol, together with glycerine and flavourings.

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"Improvements in or relating to
Tooth-whitening Compositions"

This invention concerns improvements in or relating to tooth-whitening compositions.

For mainly cosmetic reasons there is nowadays a widespread call for products that can be used to whiten teeth by removing and/or bleaching stains or other discolourations which build up on them. Products able to achieve this objective have indeed been available and much used in the United States of America for a considerable time, and more recently in Europe and elsewhere. Such long-known tooth-whitening products have all (so far as we are aware) been based on the use of peroxides as bleaching agents, typically high concentrations e.g. of about 15% by weight of hydrogen peroxide and/or carbamide peroxide.

The tooth-whitening effect of such peroxide-based products is excellent, and they have enjoyed the approval of many authorities and health-supervisory bodies in the United States and other countries, and indeed to a considerable extent they still continue to do so. Criticism has however been levelled against peroxide-based tooth-whitening products because some perceive there to be a health hazard involved in putting peroxides into the mouth, and all the more so at the relatively high concentrations e.g. 15% which have been employed to achieve an optimum tooth-whitening effect. The bleaching action of peroxides depends upon their breakdown to yield free

radicals. Even if no adverse effects from the use of peroxide-based tooth-whitening products have in practice yet been observed, it is generally considered that at the level of principle the formation of free radicals is potentially hazardous to health, as it can be supposed that such free radicals might well be detrimental to the gums and other tissues in the mouth.

Whether that criticism is justified or not is a matter still in dispute, but it has gained sufficient credence to lead the European Commission to issue an EC Cosmetics Directive (76/768EEC) which stipulates that oral-hygiene products shall not in the Community contain a percentage concentration of peroxide greater than 0.1%. That is a maximum level so low as to preclude any possibility of achieving a significant tooth-whitening effect. There is thus a need to develop some alternative tooth-whitening product, for use in at least the European market but no doubt also elsewhere, which will be of comparable efficacy to that of the known peroxide-based products but which is substantially or wholly free from peroxides and of course also otherwise satisfactory in terms especially of its stability during manufacture, transportation and storage at ambient temperature under a range of climatic conditions and of course its ability to be formulated in way that is commercially acceptable and safe in use.

The requirements for an alternative, substantially peroxide-free tooth-whitening product are in fact quite

onerous and hard to balance. Since the bleaching effect of the known peroxide-based products systems seemingly stems from their ability to oxidize, it was no doubt appropriate to search for alternative oxidizing systems... but there are a great many notionally-available oxidizing systems known to chemists, of greater or lesser oxidation potential as compared with peroxide-based systems and all of them with their own individual characteristics and limitations.

It is only by perceptive investigation and after prolonged experimentation that we have been able, rather surprisingly, to provide a solution to this intractable problem. We have now found that a safe and effective tooth-whitening product can be formulated wherein the oxidizing system is provided by the simultaneous use of both chlorate and chlorite salts, especially within defined limits, and advantageously in certain selected relative proportions.

According to this invention there are provided tooth-cleaning compositions, capable of achieving a tooth-whitening effect, which comprise in combination both non-toxic chlorate and chlorite salts together with an orally-acceptable predominantly non-aqueous carrier resistant to biodegradation.

The bleaching effect of the chlorate and chlorite salts is associated with the respective chlorate and chlorite ions, and in principle therefore one may employ any non-toxic salts thereof. However, for both

physiological and commercial reasons it is obviously preferred to employ sodium salts, thus sodium chlorate and sodium chlorite.

While higher concentrations of course are effective for tooth-whitening purposes, general safety considerations as well as cost factors usually impose a practical upper limit of chlorate content of about 5% (calculated by weight of NaClO_3). Conversely, while the chlorate does not become ineffective its activity diminishes as its concentration is reduced, and we take the view that for practical purposes the concentration of chlorate in the composition should not be below about 1%.

The concentration of chlorite may safely vary over an even wider range. We have indeed tested compositions containing as much as 25% of chlorite (by weight of NaClO_2) without observing any ill-effect. However the use of such high concentrations of chlorite shows no commensurate advantage, and if only for commercial reasons should be avoided. We prefer to employ no more than about 2% of chlorite, which we have found entirely adequate to achieve a satisfactory tooth-whitening effect, at least in combination with the chlorate. Conversely, while there is no abrupt cessation of activity as the concentration of chlorite falls, at the practical level we consider that the compositions should not contain less than 0.5% of chlorite, indeed preferably not less than 0.6% thereof.

As already hinted above, we have moreover surprisingly

found that there appears to be some kind of synergistic activity between chlorate and chlorite, which is most marked at certain relative proportions between them. We are not aware that any synergistic interaction between chlorate and chlorite as ever previously been observed, even as regards oxidizing systems envisaged for other purposes - and certainly not in any kind of pharmaceutical and/or cosmetic context.

Our discovery of this synergistic interaction was thus entirely empirical, and at first based merely upon visual observation of the effects of a large range of compositions which were under test; but it has by now been semi-established by quantitative evaluations of a scientific nature. Synergy being an elusive thing which it is not easy to prove in a wholly-convincing manner we do not wish at this stage to be limited by any theoretical considerations, but we have by now secured sufficient evidence to justify our current belief that there is such a synergistic interaction between chlorate and chlorite in the tooth-whitening compositions of this invention, and indeed that it is most pronounced within the range of relative proportions indicated below.

For the reasons indicated above, it is much preferred that the two components of the oxidizing system should be present in the compositions of this invention within the range of:

Chlorate (as NaClO_3) : Chlorite (as NaClO_2)
= from 5 : 5 to 5 : 2

and above all at or about 5 : 2.

The tooth-whitening composition of this invention is intended for use in the mouth (either as what the Americans call a "home-bleach" product for use by individuals in the domestic environment, or as what they call an "office-bleach" product for use by professional dentists and the like) and therefore should have a pH value comparable with that of the mouth.

In fact the mouth pH value in normal healthy humans is slightly alkaline, say about 7.5, and thus the composition as a whole should have a near-neutral pH value, but for various reasons we consider that a slightly acidic pH value is on balance best, so preferably the composition will be formulated overall to have a pH value in the range of from 6 to 7, conveniently about 6.5.

The chlorate-and-chlorite oxidizing system to which reference has been made above is quite effective, especially when those components are used at the preferred concentrations and relative proportions, to achieve a good tooth-whitening effect even without further assistance. The main effect of such an oxidizing system is however to bleach extrinsic staining, thus in the plaque on the teeth, and they have relatively little effect on any intrinsic staining if present. We have found however that a much

improved tooth-whitening effect against intrinsic staining can be achieved when the compositions include at least one proteolytic enzyme(s). Not all proteolytic enzymes are however equally or even at all suitable.

There are a variety of considerations which must be taken into account when selecting enzymes for use in the compositions of this invention. Such proteolytic enzymes if they are to be usable in these compositions must be oxidation-resistant. That consideration alone proved enough to exclude something like 50% of the enzymes which we initially considered. Furthermore, the activity of proteolytic enzymes is often very pH-dependent, and since as already indicated above the use of these tooth-whitening compositions in the mouth prescribes that they should be near-neutral but (perhaps for other reasons) slightly on the acidic side, one is driven to chose proteolytic enzymes which display their optimum activity in the pH range of from say 6 to 7. Such pH considerations were found to exclude perhaps another 50% of the otherwise-available oxidation-resistant enzymes.

Accordingly it is a much preferred feature of the tooth-whitening compositions of this invention that they should also contain an effective concentration of at least one oxidation-resistant proteolytic enzyme having significant activity in the pH range from 6 to 7.

Other such proteolytic enzymes can be found by application of the stated considerations, but they can

conveniently be selected from those which are commercially-available and we have tested including, for instance glucose oxidase, papain, alkaline proteinases, and neutral proteinases. We currently prefer to employ glucose oxidase, which is commercially-available under the trade name GLUCOX P200 from Rhone-Poulenc.

The amount of such proteolytic enzyme which desirably will be incorporated in the composition is of course dependent on its activity at the operating pH, but in the case of the preferred glucose oxidase we recommend that it should be present in a concentration in the range of from 0.1% w/w up to 1% w/w, and preferably at a concentration of about 0.5% w/w.

The above-described oxidizing system, preferably in conjunction with the proteolytic enzyme(s), represents the active ingredients of the composition which are effective to bring about tooth-whitening. However the compositions will also desirably include other ingredients of a more conventional nature, most of which actually serve some active function for the purposes of the invention while some however are little more than diluents, extenders and vehicles.

Since the compositions must be sufficiently stable to withstand the rigours of transportation, storage and use in even the home environment, it is near-essential that they should overall exhibit bio-static properties. Accordingly the compositions with advantage can incorporate a biostat

or biocide. Those terms however are used herein to embrace components which though not normally regarded as bio-active will serve in the composition as formulated to inhibit the growth of bio-organisms and/or to combat such micro-organisms. One such material which we have found very effective for this purpose and therefore recommend is propylene glycol, which at the kind of concentration in the composition that we recommend is effective to disrupt and even lyse the more common micro-organisms which are likely to be encountered.

We currently prefer to employ propylene glycol in the compositions at a concentration in the range from 15 to 25% w/w, desirably at about 20-22 %w/w. Although employed primarily for its bio-static effect, propylene glycol also has two other desirable attributes, firstly that it adds "body" to the formulation and secondly that it helps to impart a slight, desirable sweetness to the taste of the formulation.

At this point it is convenient to add that the composition also desirably contains a liquid bulking agent which also serves to add "body" to the composition, and this may desirably be glycerine which again (like propylene glycol) has the further advantage that it imparts a slightly sweet taste to the composition.

Of course the taste of the composition can be further enhanced by inclusion of small but effective amounts of flavouring agents e.g. peppermint oil, such flavouring

agents being usually necessary only in small fractions of a percent.

The tooth-whitening composition of this invention is in some measure akin to toothpaste, and it can advantageously include any other adjuvants regarded as desirable in toothpaste-type products. Perhaps foremost amongst these is/are suitable pigment(s) such as e.g. titanium dioxide, serving primarily as an opacifier but also of course as a bulking agent.

When pigment such as titanium dioxide is present the composition will advantageously also contain a dispersant, e.g. that commercially-available under the name DISPEX GA 40, which assists to keep the pigment particles in finally-dispersed suspension.

Any problems, e.g. in prolonged storage, arising from a tendency for the pigment particles to separate out and sediment can also be reduced or eliminated by incorporating thickening agents in the composition, e.g. xanthan gum.

In order that the invention shall be well understood one preferred embodiment of tooth-whitening composition will now be described in more detail, though by way of illustration only, in the working example set out below:

Example 1: Tooth-whitening Composition

37.288 Parts by weight of deionized water were mixed together in a main mixing vessel with 21.400 parts of propylene glycol, 0.002 part of sodium fluoride, 0.200 part of a bacteriostat (commercially-available under the trade name IRGASAN DP 300, from Ciba-Gagay), 5.000 parts of sodium chlorate and 2.000 parts of sodium chlorite, until the mixture was homogeneous.

Separately, in a secondary mixing-vessel 0.010 parts by weight of a pigment dispersant (the sodium salt of a carboxylated polymer, commercially-available under the trade name DISPEX GA 40, from) were mixed with 0.500 part of deionized water, and to that initial mixture there were then added 30.000 parts of glycerine, 0.100 part of peppermint oil, 1.000 part of titanium dioxide and 0.500 part of the proteolytic enzyme glucose oxidase. These various ingredients were added and mixed in until a smooth, homogeneous paste had been formed.

The resultant paste in the secondary mixing vessel was then added to the previously-prepared mixture in the main vessel and mixed thereinto until the resultant mix was homogeneous.

Then 2.000 parts of xanthan gum were added and mixed in batchwise, using a high-shear mixer, until the desired, smooth, homogeneous composition was thereby achieved.

The resultant composition contained the following ingredients in the following amounts:

| <u>Ingredient</u> | <u>%w/w</u> |
|-------------------|-------------|
| Deionized Water | 37.788 |
| Propylene Glycol | 21.400 |
| Sodium Fluoride | 0.002 |
| IRGASAN DP 300 | 0.200 |
| Sodium Chlorate | 5.000 |
| Sodium Chlorite | 2.000 |
| DISPEX GA 40 | 0.010 |
| Glycerine | 30.000 |
| Peppermint oil | 0.100 |
| Titanium Dioxide | 1.000 |
| Glucose Oxidase | 0.500 |
| Xanthan Gum | 2.000 |
| | ----- |
| Total: | 100.000% |
| | ===== |

CLAIMS

1. Tooth cleaning compositions, capable of achieving a tooth-whitening effect, which comprise in combination both non-toxic chlorate and chlorite salts together with an orally-acceptable predominantly non-aqueous carrier resistant to biodegradation.
2. Compositions as claimed in claim 1, in which the salts are sodium chlorate and sodium chlorite.
3. Compositions as claimed in claim 1 or 2, in which the chlorate content does not exceed 5% (calculated by weight of NaClO_3).
4. Compositions as claimed in any of the preceding claims, in which the chlorate content is not less than 1% (calculated by weight of NaClO_3).
5. Compositions as claimed in any of the preceding claims, in which the chlorite content does not exceed 25% (calculated by weight of NaClO_2).
6. Compositions as claimed in any of the preceding claims in which the chlorite content does not exceed 2% (calculated by weight of NaClO_2).
7. Compositions as claimed in any of the preceding claims, in which the chlorite content is not less than 0.5% (calculated as NaClO_2).
8. Compositions as claimed in any of the preceding

claims, in which the chlorite content is not less than 0.6% (calculated as NaClO_2).

9. Compositions as claimed in any of the preceding claims, in which the weight ratio of chlorate salt (calculated as NaClO_3) to chlorite salt (calculated as NaClO_2) is in the range of from 5:5 to 5:2.

10. Compositions as claimed in any of the preceding claims, in which the weight ratio of chlorate salt to chlorite salt is substantially 5:2.

11. Compositions as claimed in any of the preceding claims, which have a pH value in the range of from 6 to 7.

12. Compositions as claimed in any of the preceding claims, which have a pH value of substantially 6.5.

13. Compositions as claimed in claim 11 and claim 12, which also include an effective concentration of at least one oxidation-resistant proteolytic enzyme having significant activity in the pH range of from 6 to 7.

14. Compositions as claimed in any of the preceding claims, which include a concentration able to achieve a tooth-whitening effect against intrinsic staining of at least one of the following oxidation-resistant proteolytic enzymes namely glucose oxidase, papain, alkaline proteinases and/or neutral proteinases.

15. Compositions as claimed in any of the preceding claims, which includes an effective concentration of

glucose oxidase.

16. Compositions as claimed in claim 14 or claim 15 in which glucose oxidase is present in a concentration of from 0.1% w/w up to 1% w/w.

17. Compositions as claimed in claim 16, which include substantially 0.5% w/w of glucose oxidase.

18. Compositions as claimed in any of the preceding claims, which also incorporate an effective concentration of a biostat and/or biocide.

19. Compositions as claimed in claim 18, in which the biostat is or includes propylene glycol.

20. Compositions as claimed in claim 19, in which propylene glycol is present at a concentration in the range of from 15% w/w to 25% w/w.

21. Compositions as claimed in claim 20, in which propylene glycol is present at a concentration in the range of from 20% w/w to 22% w/w.

22. Compositions as claimed in any of the preceding claims, which also include one or more liquid bulking agent(s).

23. Compositions as claimed in claim 22, in which the liquid bulking agent(s) is or include glycerine.

24. Compositions as claimed in any of the preceding claims which also include flavouring agent(s).

25. Compositions as claimed in any of the preceding claims

which also include a pigment serving as both bulking agent and opacified.

26. Compositions as claimed in claim 25, which also include a dispersant to assist in keeping the pigment particles in suspension.

27. Compositions as claimed in claim 25 or claim 26, which also include a thickening agent.

28. Compositions as claimed in claim 27, in which the thickening agent is or includes xanthan gum.

29. Tooth-cleaning compositions as claimed in any of the preceding claims and substantially as herein described.

30. Tooth-cleaning compositions substantially as herein described with reference to the Example.

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| Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search report) | Application number GB 9410224.1 |
| Relevant Technical Fields (i) UK Cl (Ed.N) A5B (BFA) (ii) Int Cl (Ed.6) A61K 7/20 Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE: WPI, CAS ONLINE, PHARM, JAPIO, CLAIMS | Search Examiner MR S J PILLING |
| | Date of completion of Search 14 AUGUST 1995 |
| | Documents considered relevant following a search in respect of Claims :- 1 TO 30 |

Categories of documents

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| X: Document indicating lack of novelty or of inventive step. | P: Document published on or after the declared priority date but before the filing date of the present application. |
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| Category | Identity of document and relevant passages | Relevant to claim(s) |
|----------|--|----------------------|
| A | GB 657950 (AKTIESELSKABET DANSK ETC) page 2 lines 19 to 24 | |
| A | EP 0287074 A2 (ALCIDE CORP.) page 7 line 57 to page 8 line 57 and the Examples | |
| A | FR 2187288 A (NATIONAL PATENT DEVELOPMENT CORP.) page 1 lines 1 to 25, Example 1 and Claim 1 | |